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<b>(54) Title:</b> TROPYL 7-AZAINDOL-3-YLCARBOXYAMIDES AS ANTITUSSIVE AGENT  <b>(57) Abstract</b>  Optionally substituted pharmacologically active tropyl 7-azaindol-3-ylcarboxamides and their possible correspondent oxides, the process for their preparation and the pharmaceutical compositions containing them are described.		

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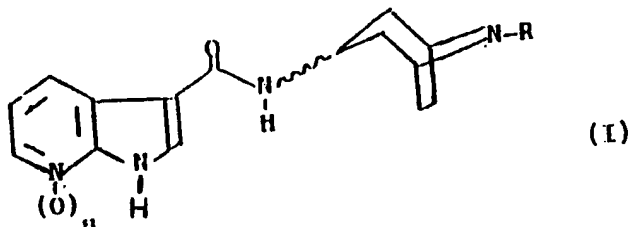
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Description**TROPYL 7-AZAINDOL-3-YLCARBOXYAMIDES AS ANTITUSSIVE AGENT**

The present invention refers to troyl  
7-azaindol-3-ylcarboxyamides of formula (I)

5



10 wherein the symbol  $\sim$  indicates that compounds (I) may have the  
configuration exo(or B-) or endo(or A-) and

R represents a hydrogen atom; a saturated linear or  
branched  $C_1-C_4$  alkyl; a  $C_7-C_9$  arylalkyl; a  
 $-(CH_2)_n-(C_3-C_7)$  cycloalkyl group wherein n is an  
 15 number between 0 and 4; a  $C_1-C_{12}$  acyl group,  
 s represents 0 or 1.

As  $C_3-C_7$  membered cycloaliphatic ring cyclopropyl, cyclopentyl  
and cyclohexyl are preferred.

As  $C_7-C_9$  arylalkyl the benzyl and the phenethyl radical are  
 20 preferred.

As  $-(CH_2)_n-(C_3-C_7)$  cycloalkyl group, the cyclopropylmethyl  
group is preferred.

As  $C_1-C_{12}$  acyl group the formyl group is preferred.

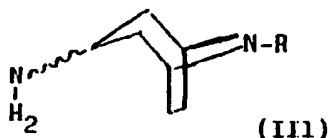
Among  $C_1-C_4$  alkyl radicals are preferred the methyl, ethyl and  
 25 isopropyl radicals.

A further object of the invention is represented by the  
compounds of formula (I) wherein the aminotroyl group is  
protected by a suitable conventional protecting group among  
which is preferred the ter-butoxycarbonyl. Also included in  
 30 the scope of the invention are the acid addition salts of the

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compounds (I) with suitable, non-toxic, pharmaceutically acceptable acids. Among these salts are cited the hydrochlorides, hydrobromides, alkyl and arylsulfonates, succinates, tartrates and citrates.

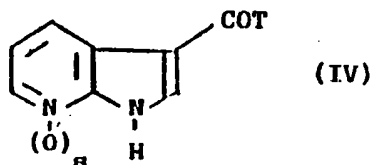
- 5 The compounds of formula (I) are obtained by reaction of a tropanylamine of formula (III):



10

wherein the symbols R and ~ have the above defined meaning, with an optionally activated azaindolyl-3-carboxylic acid (IV):

15



- wherein the symbol s, has the above mentioned meaning and T represents a hydroxy group or the residue of a carboxylic acid activating group. Preferred activating groups are those well known in the art such as, for example, chlorine, bromine, azide, imidazolide, p-nitrophenoxy, 1-benzotriazole, N-O-succinimide, acyloxy and more specifically, pivaloyloxy, Cl-C4 alkoxy-carbonyloxy, such as, for example, C<sub>2</sub>H<sub>5</sub>OCO-O-, a dialkyl- or a dicycloalkyl-O-ureide. The carboxyamides of formula (I) are isolated from the reaction mixture as free bases or as addition compounds with a suitable mineral or organic acid. When the compounds of formula (IV) are used in
- 21
- 25
- 30

their free acid form, the reaction is carried out in the presence of a condensing agent such as, for example, a carbodiimide, optionally in the presence of an activating agent such as, for example, hydroxybenzotriazole or  
5 hydroxysuccinimide, with the intermediate formation of dialkyl- or dicycloalkyl-O-ureides. Typical condensing agents are the dicyclohexyl- and the diisopropylcarbodiimide, carbodiimides soluble in an aqueous medium etc. Preferred reaction conditions are those which provide the use of  
10 equimolar amounts of the reagents, in inert solvents such as ethyl acetate, aromatic hydrocarbons such as benzene and toluene, cycloalkanes such as cyclohexane, dioxane, tetrahydrofuran, dimethylsulfoxide, dimethylformamide, N-methylpyrrolidone, acetonitrile and the mixtures thereof,  
15 operating at a temperature between room temperature and the reflux temperature of the mixture, preferably at 50-60°C.

The bicyclic tropanylamines (III) are generally well known and also commercially available compounds. They may be prepared using methods known in the art; see for example, the method  
20 for the preparation of 3 $\alpha$ -tropanylamine of S.Archer et al., J. Amer. Chem. Soc., 79, 4194, 1957 and the method described for the preparation of 3 $\beta$ -tropanylamine R.Willstätter et al., Chem. Ber., 31, 1202, 1898, S.Archer et al., J.Amer. Chem. Soc., 80, 4677, 1858, and also A.Stoll et al., Helv. Chim. Acta 38, 559,  
25 1955; further preparations of said tropanylamines are described by P.Dostert et al., FR 2.449.570 (13.8.1982) C.A. 98, 126444q (1983); P. Donatsch et al., DE 33 22754 (29.12.1983); M.Langlois et al., FR 2.548.666 (11.01.1985) C.A. 103, 123757e (1985); E.A.Watts PCT WO 85 00.170 (17.01.1985) C.A. 103  
30 123376e (1985); D.Lednicer et al., EP 147.044 (03.07.1985)

C.A. 104 1949 1986.

The preparation of the 1H-pyrrole[2,3-b]pyridine-3-carboxylic acid 7-oxide, as well as a general procedure for the preparation of 1H-pyrrole[2,3-b]pyridine 7-oxide, has been  
5 described by S.W.Schneller et al., (J.Org. Chem., 45, 4045, 1980).

The preparation of the 1H-pyrrole[2,3-b] pyridine-3-carboxylic acid as well as the ethyl ester thereof have been described by M.M. and B.L. Robinson on J. Amer. Chem. Soc., 78, 1247, 1956.

10 In general, 7-azaindoles and their homologues 1- or 2-substituted or 1- or 2-disubstituted, for the preparation of which see for example, R.R.Lorenz et al., J.Org. Chem., 30, 2531, 1965 and references cited therein, may be converted by a Mannich reaction into their corresponding 3-dialkylaminomethyl  
15 derivatives and then transformed in the corresponding 3-formyl-7-azaindoles which, substantially according to the above mentioned procedure of M.M. and B.L. Robinson, are converted into their corresponding esters and carboxylic acids.

20 More particularly it has been found that, in a halogenated solvent and in the presence of a suitable catalyst such as aluminum chloride, i.e. in Friedel-Krafts conditions, the 7-azaindoles themselves react with a trihaloacetylhalides, preferably trichloroacetylchloride, to give, with a yield almost  
25 quantitative, the corresponding 3-trihaloacetyl-7-azaindoles such as, for example,

3-trichloroacetyl-1H-pyrrole[2,3-b]pyridine which, with further treatment with bases, such as potassium hydroxide, undergo the haloformic transposition into the corresponding  
30 7-azaindoly-3-carboxylic acids.

The following Examples are given by way of better illustrating the invention without limiting it.

Example 1

5 N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-azaindolyl-3-carboxamide (Compound A)

In an inert gas atmosphere and under stirring, a solution of 5.4 ml of trichloroacetyl chloride in 27 ml dichloromethane is added in the course of 10 minutes to a suspension of 6.8 g aluminum chloride in 54 ml dichloromethane cooled to -78°C. It  
10 is maintained at this temperature for 15 minutes then warmed up to -40°C, maintaining under stirring for a further 45 minutes. A solution of 2 g 7-azaindole in 10 ml dichloromethane is then added, stirred for 15 minutes at -40°C and the temperature is allowed to rise to 0°C and stirring  
15 continued for a further hour. Milliliters 26 of an aqueous solution of 1N hydrochloric acid are added carefully maintaining the temperature between 0 and 15°C; after decomposition of the reagents, the phases are separated and the organic phase is washed with water and treated under strong stirring with sodium bicarbonate heptahydrate to obtain  
21 a white crystalline solid which is filtered and it gives 2.6 g 3-trichloroacetyl-1H-pyrrole-[2,3-b]pyridine melting at 260°C (with decomposition). The so obtained compound is suspended in 15 ml of a 10% potassium hydroxide aqueous solution and the  
25 suspension is kept under strong stirring until complete dissolution. By acidification of the solution to pH 3-4 with a 37% hydrochloric acid aqueous solution, 1.5 g 7-azaindolyl-3-carboxylic acid separate by precipitation, melting point 230-240°C (with decomposition).

30 To a solution of 1.5 g 7-azaindolyl-3-carboxylic acid in 24 ml

of a mixture 1:1 of tetrahydrofuran:dimethylformamide, 1.29 g endo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylamine and 2.1 g dicyclohexylcarbodiimide are added.

The mixture is heated for 3 hours at 50°C, then it is  
5 evaporated to small volume, acidified with 2N hydrochloric acid and filtered removing the dicyclohexylurea precipitate. The filtrate is saturated with sodium chloride and after being made alkaline to pH 11 with sodium hydroxide, it is extracted with chloroform and it gives, by evaporation of the solvent  
10 and crystallization of the residue from ethyl ether, 1.24 g N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-azaindolyl-3-carboxamide melting at 273°C (Compound A). Operation is carried out according to the previously described procedure and using instead of endo-8-methyl-8-azabicyclo  
15 [3.2.1]oct-3-ylamine, 1-azabicyclo[2.2.2]oct-3-yl-amine, N-(1-azabicyclo[2.2.2]oct-3-yl)-7-azaindolyl-3-carboxamide melting at 275-280°C is obtained (Compound B).

#### Example 2

N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-  
20 -yl)-7-azaindolyl-3-carboxamide 7-oxide.

To a solution of 1.5 g 7-azaindolyl-3-carboxylic acid 7-oxide in 30 ml acetonitrile, 2 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride are added in portions.

After 15 minutes of stirring, a solution of 1.29 g 3  
25  $\alpha$ -tropyamine in 10 ml of acetonitrile is added. It is kept at room temperature for 2 hours, heated to 50°C for 2 hours, concentrated under vacuo to a third of its volume and diluted with 100 ml of water. After several extractions with ethyl acetate, the organic phases are collected together and  
30 evaporated to dryness. The residue is purified by



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chromatography over silica gel ( $\text{CHCl}_3$ :MeOH) to give 1.12 g  
N-(8-methyl-8-azabicyclo[3.2.1]oct-3 $\alpha$ -  
-yl)-7-azaindolyl-3-carboxamide 7-oxide.

Example 3

5 N-(8-cyclopropylmethyl-8-aza-bicyclo[3.2.1]oct-3 $\beta$ -yl)-7-azaind  
olyl- 3-carboxamide.

A solution of 2.9 g N-hydroxysuccinimide in 10 ml  
tetrahydrofuran is added to a solution of 1.84 g  
7-azaindolyl-3-carboxylic acid in 30 ml of a 1:1  
10 tetrahydrofuran and dimethylformamide mixture cooled to 0°C  
and under stirring. A solution of 2.1 ml  
morpholynethylisonitrile in 10 tetrahydrofuran ml is dripped  
therein and stirring is maintained for a further two hours to  
room temperature. It is diluted with 5 volumes of water,  
15 tetrahydrofuran is removed by evaporation under vacuum, it is  
acidified to pH 3-4 with a potassium acid sulphate aqueous  
solution and extracted with ethyl acetate. From the collected  
together organic extracts, by evaporation of the solvent, 2.6  
g 7-azaindolyl-3-carboxylic acid succinimide ester  
20 crystallizes.

Grams 1.02 of the so obtained succinimide ester are dissolved  
at room temperature and in argon atmosphere in 7.5 ml  
acetonitrile and to the solution 5 ml of a solution of 0.75 g  
3 $\beta$ -amino-8-cyclopropylmethyl-8-azabicyclo[3.2.1]octane in 0.5  
25 ml acetonitrile are added. After 8 hours, the mixture is  
concentrated under vacuum to small volume and diluted with a  
sodium bicarbonate saturated solution until a slight alkaline  
pH. It is extracted four times with 20 ml each of ethyl  
acetate and from the collected together extracts, after  
30 evaporation of the solvent and crystallization from ethyl

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ether, 1.5 g of N-(8-cyclopropylmethyl-8-aza-bicyclo[3.2.1]oct-3 $\beta$ -yl)-7-aza-indolyl-3-carboxiamide are obtained.

In a similar manner by reaction with the suitable  
5 3-amino-8-azabicyclo[3.2.1] octane are obtained:

- N-(8-cyclopropylmethyl-8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-formyl-8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-carboxyamide;
- 10 - N-(8-tert-butoxycarbonyl-8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-phenylethyl-8-azabicyclo[3.2.1]oct-3 $\alpha$ -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-benzyl-8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-  
15 carboxyamide;
- N-(8-cyclohexylmethyl-8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-cyclopentylmethyl-8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-carboxyamide;
- 20 - N-(8-ethyl-8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-isopropyl-8-azabicyclo[3.2.1]oct-3 $\alpha$ -yl)-7-azaindolyl-3-carboxyamide.

#### Example 4

25 N-(8-azabicyclo[3.2.1]oct-3  $\alpha$  -yl)-7-azaindolyl-3-carboxyamide tri-fluoroacetate.

A solution of 0.3 g N-(8-tert-butoxycarbonyl-8-azabicyclo[3.2.1] oct-3 $\alpha$ -yl)-7-azaindolyl-3-carboxyamide in 2 ml of dichloromethane and 2 ml of trifluoroacetic acid is  
30 maintained for 8 hours at room temperature then the reaction

mixture is evaporated to dryness under vacuum and the residue, crystallized from ethyl ether:hexane, and it gives the trifluoro acetate of N-(8-azabicyclo[3.2.1]oct-3-yl)-7-azaindolyl-3-carboxamide.

5 Benzoyl N-quinuclidinylamides and N-tropylamides and analogous amides of aryl- and heteroarylcarboxylic acids represent compounds which in the last decade were the object of wide researches having as aim the identification and the functional characterization of the subtypes of the serotonin (5-HT)  
10 receptor and the realization of ligands having high bond affinity and high receptor specificity. Substances belonging to the same family of compounds have resulted clinically effective in the control of the emesis induced by antitumoral chemotherapy, a pharmacological event which was supposed to be  
15 modulated by 5-HT<sub>3</sub> receptors in the area postrema. Lastly there are pharmacological indications which make believe that these substances because they are 5-HT<sub>3</sub> antagonists, may be useful in correcting affections of the central nervous system, such as, for example, schizophrenia, anxiety or the loss of  
20 memory, since 5-HT<sub>3</sub> receptors also seem to modulate the cholinergic neurons.

Specific examples of 5-HT<sub>3</sub> antagonists are, for example, Ondasetron, BRL 24682 or N-(endo-8-methyl-8-azabicyclo-  
[3.2.1]oct-3-yl)-2-methoxy-4-amino-5-chlorobenzamide, ICS-205-  
25 930 or (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)indolyl-3-carboxylate.

More recently, both quinuclidyl- and troyl-amides of the 7-methyl- 8-azaindolyl-3-carboxylic acid (T.Higashino et al., Toyo Jozo Co., EP 483 836 (06.05.1992), C.A. 117 171436K and  
30 2-methylimidazo[1,2-a] pyridin-3-carboxylic acid (K.Nitta et

al., Mitsubishi Kasei Corp. JP 01258679 (16.10.1989), C.A. 112  
 178986v) have been described as 5-HT<sub>3</sub> antagonists and  
 therefore are useful as antiemetic, in the prevention of  
 nausea by cis-Platin and, more in general, as  
 5 antiserotonergic drugs to be used for the treatment of the  
 migraine and anxiety.

The amides of the 7-azaindol-3-carboxylic acid (F.D.King,  
 Beecham Group, EP 254 584 (27.01.1988) C.A. 109 93018u) have  
 also been described as 5-HT<sub>3</sub> -antagonists. Lastly, more  
 10 recently, M.Kato et al. (Fujisawa Pharmac., JP 04021681  
 (24.01.1991) C.A. 116 255499a) describe  
 pyrrolpyridinecarboxyamides of azabicycloalkylamines as  
 typical 5-HT<sub>3</sub> antagonists with particular mention to the  
 amides of 3-amino-8-methylazabicyclo[3.2.1]octane with  
 15 1-methyl and 1-ethyl-7-azaindoly-3-carboxylic acids.

Compounds A and Compounds B of the present invention, which  
 are examples of endo-tropyl and quinuclidylamide of  
 7-azaindoly-3-carboxylic acid respectively have been studied  
 "in vitro" for their interaction with the 5-HT<sub>1</sub>, 5-HT<sub>2</sub> and  
 20 5-HT<sub>3</sub> receptors.

Table I

Binding Test:	5-HT <sub>1</sub>	5-HT <sub>2</sub>	5-HT <sub>3</sub>
	% of inhibition at 3.6 10 <sup>-5</sup> M		IC <sub>50</sub> <sup>M</sup>
25 Ondasetron	7.6	21.7	3 10 <sup>-9</sup>
Compound A (7-azaindoly-3-carboxy tropylamide)	0.0	8.6	3 10 <sup>-6</sup>
30 Compound B (7-azaindoly-3-carboxy quinuclidylamide)	37.0	3.9	3 10 <sup>-7</sup>

From the above study a first indication of an atypic behaviour of 7-azaindoly-3-carboxylic acid trotylamides when compared to the corresponding quinuclidylamid surprisingly appeared.

The interaction of Compounds A and B with other receptors ( $\alpha_1$ ,  $\alpha_2$ , benzodiazepine (o bzd), GABA A,  $\sigma$ ) in comparison to the typical 5-HT<sub>3</sub> antagonist Ondastron and BRL 24682 has been studied and for each case the displacement % of the single selective ligand from the corresponding receptor at concentration  $10^{-5}$  M of the compounds under examination, has been evaluated.

Table II

Displacement percentage					
Receptors:	$\alpha_1$	$\alpha_2$	bdz	Gaba A	$\sigma$
Ondasetron	72	30	*	38	45
BRL 24682	28	16	98	89	0
Compound A	13	*	*	83	70
Compound B	7	*	*	6.7	26

\* not active: no capacity of displacement of the ligand at a conc.  $10^{-8}$  M.

The disparity in behaviour between 7-azaindoly-3-carboxylic acid quinuclidyl- and trotyl-amides results even more evident from the above-listed data. 7-Azaindoly-3-carboxamide (Compound A) shows a very weak interaction with 5-HT<sub>3</sub> receptors: 1,000 times lower than that of Ondasetron, which is a typical 5-HT<sub>3</sub> antagonist, and logarithmically lower than that of Compound B. Compound A itself shows surprisingly an unusual ability of a double interaction, apparently selective, towards GABA A and  $\sigma$  receptors, which ability is definitely weak or absent in the

corresponding quinuclidylamide and, to the contrary, it seems aspecific in 5-HT<sub>3</sub> antagonist Ondasetron.

As to the other 5-HT<sub>3</sub> antagonist, BRL 24682, it is evident its high interaction with the benzodiazepine and GABA A receptors,

- 5 and its complete lacking of interaction with the receptors, thus allowing to exclude that the selective interaction of 7-azaindolyicarboxytropylamide (Compound A) with GABA A and  $\sigma$  receptors be a characteristic generally present in potential 5-HT<sub>3</sub> antagonists, or, at least in substances so defined on  
10 the basis of a simple chemical structure analogy.

Besides these differences "in vitro" on the receptor behaviour great differences has been evidenced "in vivo" in the tussive stimulus inhibition provoked by inhalation of irritant citric acid as well as capsaicine aqueous solutions.

- 15 The compounds have been tested in guinea pigs in comparison to codeine, used as standard compound, at the single dose of 100 mg/kg according to the technique of Charlier et al., (Arch. Int. Pharmacodyn., 134, 306, 1961) which has been slightly modified.

- 20 The percent reduction evaluated in the number of short coughs after administration of the compound under examination taken in comparison to the number of short coughs observed in each of the animals to which the compound was administered, have been noted.

- 25 For each of the compounds under examination it has been also tested the effect on the increase of the sleeping time induced by barbiturates. The test was carried out on mice by oral administration of a single dose of 100 mg/kg of the compound. The data obtained are listed in the following Table III.

Table III

		% INHIBITION of the coughing stimulus by:		%
		ac. citric	capsaicin	sleeping time increase
5				
	Ondasetron	30.5	50.5	- 8*
	BRL 24682	44.1	n.d.	+ 34.8
	Compound A (7-azaindolylcarboxy tropyamide)	61.7	76.30	- 28.9
10				
	Compound B (7-azaindolylcarboxy quinuclidylamide)	46.0	21.0	- 7
	Codeine	63.2	58.4	+ 106.4
15	* at the dose of 10 mg/kg                      n.d.: not determinable			

In a successive study, carried out at different doses, using as comparison compounds typical antitussive compounds commonly used in therapy, either having a central effect, i.e. codeine, or having a peripheral effect, i.e. levodropropizine, it has been observed that the protecting antitussive effect of 7-azaindolylcarboxytropylamine (Compound A) depends on the dose administered. For these compounds as well as for the most interesting reference compounds the dose inhibiting 50% of the short coughs ( $ID_{50}$ ) induced either by citric acid or capsaicine has been determined.

Table IV

$ID_{50}$ in mg/kg os (95% confidence) Coughing stimulus			
30	Ac. citric	Capsaicin	2N H <sub>2</sub> SO <sub>4</sub>

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Levodropropyzina	151 (126-180)	145 (84-252)	265 (168-240)
Codein	65 (57-74)	74 (52)107)	102 (55-190)
Ondasetron	209 (126-349)	97 (36-261)	- - -
5 Compound A	57 (41-80.5)	51 (33-77)	- - -

- - - not tested

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In both pharmacological tests only  
7-azaindoly-3-carboxy-endo-N-tropylamide (Compound A) showed  
10 to be effective. Compound A proved to be at least equiactive  
as codeine, and advantageously in respect to the latter, it  
does not show any increase of the sleeping time induced by  
barbiturates.

It is assumed that Capsaicine releases substance P from the  
15 peripheral nerve endings of the sensitive fibers C and  
determines the necrosis of the same. It is known that  
capsaicine administration provokes the formation of an exudate  
(extra vasation by capsaicine) which can be evaluated by  
concomitant Evans bleu administration.

20 Solely Compound A and not Ondasetron has been found to give a  
42% protection (in comparison with non-treated animals) from  
capsaicine extravasation when the compounds are administered  
at 10 mg/kg dosage by intraperitoneal route. A similar  
protection has been observed after  
25 cis-2-benzhydryl-1-azabicyclo-[2.2.2]octane-3-(2-methoxybenzyl  
amine (CP 96 345, a non-peptide antagonist of substance P)  
administration at 10 mg/kg i.p.. It is worth to underline that  
the same substance CP 96 345 has been found to protect guinea  
pigs from cough induced by capsaicin being a 26 and 42% short  
30 cough inhibition evaluated after intraperitoneal



administration of 10 and 40 mg/kg respectively.

The compounds of the invention can be then therapeutically employed as antitussive agents without the limitation of the opiate ligand antitussive drugs like as codeine. They are  
5 useful in the treatment of coughs of different origin particularly against tussive manifestations mediated by substance P.

More particularly the compounds of the present invention are helpful to prevent nocturnal cough stimuli, due to the  
10 administration of ACE-inhibitors, widely used in the hypertension treatments of which conditions the nocturnal cough represents a side effect which is hard to cure.

The compounds of the invention are also useful in the treatment of inflammatory conditions and more generally of  
15 those pathological conditions in which substance P and other neuropeptides have a conclusive etiological part and moreover in asthmatic conditions and pain of neurological origin.

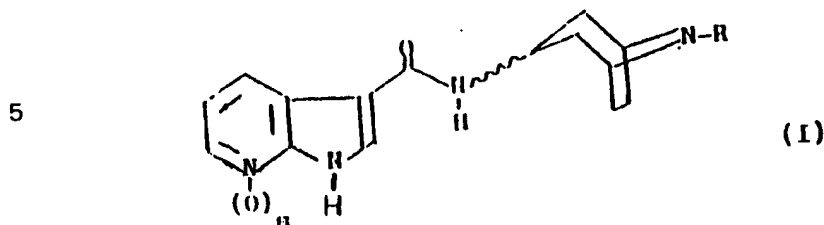
The compounds of the invention may be administered by oral, sublingual, endovenous, subcutaneous, intramuscular, rectal  
20 route and by inhalation. The preferred doses vary from about 0.05 to about 15 mg/kg/die, depending on the conditions, weight, age of the patient and on the administration route. Higher dosages of the compounds of the invention, even for a prolonged period of time, have no contraindication because of  
25 their very low toxicity. Compound A LD<sub>50</sub> in mice is 1 g/kg by oral route.

The compounds of the invention may be therapeutically used in most of the pharmaceutical preparations, using conventional techniques and excipients as are described in "Remington's  
30 Pharmaceutical Sciences Handbook" Hack Publ.Co.New York, USA.

These compositions include capsules, tablets, drinkable solutions, suppositories, vials for parenteral route and by inhalation, systems with controlled release and similar.

Claims

1. Tropol 7-azaindol-3-ylcarboxyamides of formula (I)



wherein the symbol  $\sim$  indicates that compounds (I) may have the configuration exo(or  $\beta$ -) or endo(or  $\alpha$ -) and

10 R represents a hydrogen atom; a saturated linear or branched  $C_1-C_4$  alkyl; a  $C_7-C_9$  arylalkyl; a  $-(CH_2)_n-(C_3-C_7)$  cycloalkyl group wherein n is an number between 0 and 4; a  $C_1-C_{12}$  acyl group, s represents 0 or 1

15 and the corresponding non-toxic pharmaceutically acceptable acid addition salts.

2. N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-azaindolyl-3-carboxamide.

3. A pharmaceutical composition having antitussive activity  
20 which contains a therapeutically effective quantity of a compound according to claims 1 and 2 in mixture with suitable pharmaceutically acceptable diluents.

4. A pharmaceutical composition useful for the treatment of asthmatic conditions and neurological origin algesia wich  
25 contains a therapeutically effective quantity of a compound according to claims 1 and 2 in mixture with suitable pharmaceutically acceptable diluents.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 94/00234

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D519/00 A61K31/46

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992, Columbus, Ohio, US; abstract no. 255499a, KATO, MASAYUKI ET AL. 'Preparation of pyrrolopyridine derivatives as 5-HT antagonists.' see abstract * RN 141650-61-5, -60-4, -59-1, -58-0, -56-8 * & JP,A,9 221 681 (FUJISAWA PHARMACEUTICAL CO.)	1
A	EP,A,0 504 679 (G.D. SEARLE & CO.) 23 September 1992 see claims --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

21 September 1994

Date of mailing of the international search report

- 3. 10. 94

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# INTERNATIONAL SEARCH REPORT

I: ational Application No

PCT/IB 94/00234

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	EP,A,0 581 165 (DOMPE' FARMACEUTICI S.P.A.) 2 February 1994 see claims -----	1,3

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/IB 94/00234

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP-A-9221681		NONE	
EP-A-0504679	23-09-92	US-A- 5260303 AU-A- 1572892 EP-A- 0530353 JP-T- 6500124 WO-A- 9215593	09-11-93 06-10-92 10-03-93 06-01-94 17-09-92
EP-A-0581165	02-02-94	NONE	